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10/584,028	06/22/2006	Nobuyuki Takakura	1254-0318PUS1	4443

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER
KIM, TAEYOON

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
11/26/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/584,028	TAKAKURA ET AL.	
	Examiner	Art Unit	
	TAEYOON KIM	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-22* is/are pending in the application.

4a) Of the above claim(s) *20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 June 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/10/07; 6/22/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 12-22 are pending.

Election/Restrictions

Applicant's election with traverse of Group I (claims 12-19) in the reply filed on 10/22/2008 is acknowledged. The traversal is on the ground(s) that there is no serious burden to search and examine the entire application.

Applicant alleges that there would be no burden on the examiner in examining all of the claims at once, relying on M.P.E.P. §803. Chapter 800, however, is limited to a discussion of the subject of restriction and double patenting under Title 35 of the United States Code and Title 37 of the Code of Federal Regulations as it relates to national applications filed under 35 U.S.C. 111(a). The discussion of unity of invention under the Patent Cooperation Treaty Articles and Rules as it is applied as an International Searching Authority, International Preliminary Examining Authority, and in applications entering the National Stage under 35 U.S.C. 371 as a Designated or Elected Office in the U.S. Patent and Trademark Office is covered in M.P.E.P. §1850 and is dictated by PCT Rules 13.1 and 13.2. See M.P.E.P. §801. Burden is not a consideration in a finding of lack of inventive unity; rather, according to M.P.E.P. §1850, the only consideration is whether the inventions share a special technical feature.

It is acknowledged that applicant elected EGF as a species. Since the listed species in claim 15 are categorized as a family of each cytokine, thus, the "EGF family" has been examined.

The requirement is still deemed proper and is therefore made FINAL.

Claims 20-22 are withdrawn from consideration as being drawn to non-elected subject matter. Claims 12-19 have been considered on the merits.

Specification

The disclosure is objected to because of the following informalities: The specification discloses the range of the ratio of 0.1:1 to 1:10 (p. 3 and 7). Since the ratio of 0.1:1 is identical to 1:10, and considering the disclosure of the preferential ratio being 1:4 in the specification, the range disclosed in the specification appears to be in error (see claim objection below). Appropriate correction is required.

Drawings

The drawings are objected to because the contents of Figs. 2, 3A, 3B, 6, 8A and 9B are invisible. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as “amended.” If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either “Replacement Sheet” or “New Sheet” pursuant to 37 CFR 1.121(d). If the changes are not accepted by the

examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claim 18 is objected to because of the following error: the range of a ratio of 0.1:1 to 1:10 appears to be incorrect. The ratio of 0.1:1 is identical to 1:10, and considering the disclosure of the preferential ratio being 1:4 in the specification (p.3 and 7), the range disclosed in claim 18 appears to be in error. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 15, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Umezawa et al. (US 2002/0142457; IDS ref.) in view of Rangappa et al. (2003, Ann. Thorac. Surg.) in further view of Egger et al. (2004, Nature), Bonnet (2003, Clin. Exp. Med), Gilmore et al. (2000, Exp. Hematol.) and Lee et al. (2004, Blood).

Umezawa et al. teach a method of differentiating multipotential stem cells from bone marrow or umbilical cord blood derived cells into cardiomyocyte in vitro (para. 11, 12, 17-19).

Umezawa et al. teach that the cells having the potential to differentiate into cardiomyocytes are cultured for 24 hours in the presence of 5-azacytidine, and then further cultured for 2-3 weeks to obtain cardiomyocytes (para. 134), satisfying the limitation of claim 13.

Umezawa et al. teach the expression of a-skeletal actin and a-cardiac actin (sarcomeric actin) in the cardiomyocytes differentiated from bone marrow (para. 330), and thus meet the limitation of claim19.

Umezawa et al. do not teach co-culture of fat tissue derived cells or a culture supernatant of the fat tissue-derived cells with bone marrow cells or cord blood derived cells, respectively.

Rangappa et al. teach a method of differentiating fat-derived mesenchymal stem cells (MSCs) into cardiomyocytes (Abstract).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to combine bone marrow or cord blood derived multipotential stem cells of Umezawa et al. with adipose-derived stroma stem cells of Rangappa et al. in the method of myocardial differentiation of the MSCs. This is because the method of differentiating bone-marrow or cord-blood derived mesenchymal stem cells into cardiomyocytes of Umezawa et al. is identical to the method of differentiating adipose-derived stromal MSCs of Rangappa et al. such that both methods utilize 5-azacytidine to induce the mesenchymal stem cells into cardiomyocytes (para. 12 and 43 of Umezawa et al., and p.776, right col. of Rangappa et al.). Since both bone marrow or cord blood derived multipotential stem cells and fat-tissue derived MSCs can be differentiated into cardiomyocytes upon the treatment with 5-azacytidine (a cardiomyogenic differentiating factor), the combined stem cell populations would be also differentiated into cardiomyocytes under the same method steps.

It is well established that duplicating components with similar functions within a composition is obvious; see *In re Harza*, 274 F.2d 669, 124 USPQ 378 (CCPA 1960) and M.P.E.P. § 2144.04. The multipotential stem cells of bone marrow or cord blood,

and MSCs of fat tissue are considered to have similar functions to differentiate into cardiomyocytes, it would have been obvious to combine two cell populations in the method of differentiating into cardiomyocytes.

With regard to the limitation of "without genetic engineering", the treatment with 5-azacytidine to the mesenchymal stem cells is not considered as a genetic engineering. Rather it is considered as epigenetic modification since 5-azacytidine is a DNA methylation inhibitor according to Egger et al. (Abstract and Table 2).

With regard to the limitation of using a culture supernatant of fat tissue-derived cells in the method of differentiating bone marrow cells or cord blood-derived cells, Umezawa et al. teach that the differentiation of cells having a potential to differentiate into cardiomyocytes can be induced by a culture supernatant of such cells (para. 105, 106, 132). Since the fat tissue-derived MSCs of Rangappa et al. is considered as a cells having a potential to differentiate into cardiomyocytes, it would have been obvious to a person of ordinary skill in the art to use a cell culture supernatant of MSCs derived from fat tissues of Rangappa et al. in the method of Umezawa et al. utilizing a culture supernatant in induction of differentiation of bone marrow cells or cord blood-derived cells into cardiomyocytes.

With regard to the limitation of using cytokines in the method of claims 14 and 15, Umezawa et al. teach the use of growth factors or cytokines such as PDGF, FGF-8 (EGF family member), ET-1 or BMP-4 for differentiation of the mesenchymal stem cells into cardiomyocytes (para. 46-48).

With regard to the limitation to the bone marrow cells being MSCs or HSCs in

claim 16, it is well known in the art that bone marrow cells comprise both HSCs and MSCs according to Bonnet (entire document), and thus the multipotential stem cells of bone marrow of Umezawa et al. inherently comprise HSCs as well as MSCs.

With regard to the limitation of ratio between bone marrow cells and fat tissue derived cells being 1:10 in claim 18, it would have been obvious to a person of ordinary skill in the art to optimize the ratio between bone marrow cells and fat tissue derived cells for the method of Umezawa et al. in view of Rangappa et al. This is because a person of ordinary skill in the art would recognize that the mixing ratio between two groups of cell population in co-culture system would be considered as a result effective variable for the method. The variables would be routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by those references. Generally, differences in concentration, and thus the ratio of the contents, will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the

motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); ** In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made especially in the absence of evidence to the contrary.

With regard to the limitation to the cord blood-derived cells being mononuclear cells in claim 17, Umezawa et al. is silent which cells the multipotential stem cells (mesenchymal stem cells) of umbilical cord blood is derived from. However, it is well known in the art that multipotential stem cells, including HSCs and MSCs according to Bonnet, can be derived from umbilical cord blood-derived mononuclear cells according to Gilmore et al. (p.1298, Materials and Method) and Lee et al. (see p.1670, MSC isolation and culture). Thus, the multipotential stem cells of Umezawa et al. would be inherently derived from mononuclear cells of umbilical cord blood.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAEYOON KIM whose telephone number is (571)272-9041. The examiner can normally be reached on 8:00 am - 4:00 pm ET (Mon-Thu).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number

for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Taeyoon Kim/
Examiner, Art Unit 1651